ORIGINAL ARTICLES

THE ETIOLOGY OF YELLOW FEVER.*

A Supplemental Note.

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In former contributions to this subject, we have shown by observations made on human beings that yellow fever may be produced in the nonimmune individual either by the bite of the mosquito[1] (genus stegomyia) that has previously been permitted to fill itself with the blood of a patient suffering with yellow fever, during the first three days of the attack, or by the subcutaneous injection of a small quantity of blood[2] (.5 to 2 cc.) drawn from the general circulation of such a patient during the active stage of this disease. For further particulars regarding these observations the reader is referred to the original papers.

Although these experiments have demonstrated that the specific agent of yellow fever is present in the blood, we may say that the prolonged microscopic search which has been made by other investigators, as well as by ourselves, both with fresh and stained preparations of blood, taken at various stages of this disease and during early convalescence, has proved thus far entirely negative. We may add that the efforts which we have made with reasonable hope of reward, both in the bodies of infected mosquitos, dissected in the fresh state, as well as by serial sections of the hardened insect, have likewise given no results which we consider worthy of record at the present time. Leaving out of consideration, therefore, for the time being, the further microscopic search for the specific agent in the blood of the sick and in the bodies of infected mosquitos, we desire to call attention to some additional observations bearing on the etiology of the disease, which one of us (Carroll) has recently made at Las Animas Hospital, Havana, Cuba, and at Columbia Barracks, near Quemados, Cuba.

We here desire to express our sincere thanks to Dr. Wm. H. Welch, of the Johns Hopkins University, who, during the past summer, kindly called our attention to the important observations which have been carried out in late years by Loeffler and Frosch relative to the etiology and prevention of foot-and-mouth disease in cattle. In the course of their investigations concerning a reliable method of immunization in this disease, the authors had occasion to dilute and afterward to pass several times through a porcelain filter, lymph which had been collected from the blebs present in the mouth and on the feet of cattle sick with foot-and-mouth disease.[3]

These observers having already ascertained that immunity could be conferred upon cattle by the subcutaneous or intravenous injection of $\frac{1}{4}\frac{1}{0}$-$\frac{1}{5}\frac{1}{0}$ cc. of pure lymph previously mixed with 1 cc. of the defibrinated blood of an animal that had recently recovered from the disease, desired to find out whether the injection into calves of given quantities of this filtered and bacteria-free lymph would not, also, enable them to confer immunity of, perhaps, a higher degree upon cattle.

The results were quite surprising, since it was shown that calves which had received $\frac{1}{1}\frac{1}{0}$-$\frac{1}{4}\frac{1}{0}$ cc. of the diluted and filtered lymph developed foot-and-mouth disease just as promptly as calves that had been injected with corresponding quantities of the unfiltered lymph.

According to Loeffler and Frosch, there were two possible explanations of this remarkable result; either that the filtered lymph held in solution an extraordinarily active toxin, or that the specific agent of the disease was so minute as to pass through the pores of a filter which prevents the passage of the smallest known bacteria.

The authors accept the latter explanation, since they were able, in later experiments,[4] by means of the filtered lymph to convey the disease through a series of six animals, the last of which sickened just as promptly after the injection of the filtered lymph, as the first of the series.

Having, therefore, conclusively determined that the microorganism of foot-and-mouth disease of cattle is so extremely minute as to pass readily through a porcelain filter, it was natural that Loeffler and Frosch should have put forward the suggestion that, perhaps, the specific agent of some of the acute infectious diseases of man and animals, such as smallpox, scarlet fever, measles, rinderpest, etc., might also belong to this group of ultra-microscopic organisms.

It was for the purpose of ascertaining whether observations conducted along the same lines as those above mentioned, might throw additional light upon the etiology of yellow fever, that the following experiments were undertaken.

Of course it will be thoroughly appreciated that in experimentation on human beings, aside from the grave sense of responsibility, at times well-nigh insupportable, which the conscientious observer must always feel, even with the full consent of the subjects to be experimented upon, there must be added another factor, viz., the difficulty of finding willing and suitable nonimmune individuals for experimentation just at the proper and urgent moment. It so happened that on the day of Dr. Carroll's arrival at Havana, August 11, 1901, the first patient of the series of seven cases of yellow fever which Dr. Guitéras[5] had produced by bites of infected mosquitos, was taken sick. The fatal termination of three of these cases produced a somewhat panicky feeling toward experimental yellow fever among the nonimmunes at Havana, which feeling was intensified by the sensational and distorted statements in one of the local Spanish papers. It was, therefore, extremely difficult—in fact, practically impossible—to obtain for inoculation purposes persons who could with reasonable certainty be regarded as nonimmunes.

Further, as it was not practicable to withdraw blood from any case of yellow fever under treatment in the city of Havana, it became necessary to produce cases by means of the bites of infected mosquitos—*Stegomyia fasciata*—accepting such subjects as were willing to submit to this mode of inoculation. In all six individuals, supposedly nonimmunes, were bitten by mosquitos; of whom four gave a negative and two a positive result.

The following are the negative cases:

August 14, 1901, S. V., Spaniard, resident of Havana for a few months, was bitten by two insects that had been applied to a yellow fever patient 34 days previously. Result negative, although the bites of two mosquitos from this same lot had already infected an individual, who later died of yellow fever.

September 5, 1901, J. T., American, was bitten by nine insects that had been applied to a mild case of yellow fever on the second day of the attack, 23 days before. He was again bitten 30 days later by four mosquitos that had been applied to a moderately severe case of experimental yellow fever 11 days before. The result of both inoculations was negative. This man had resided one year in Central America, and we were afterwards informed that he had confessed to a previous attack of the disease.

September 11, 1901, A. P., Spaniard, was bitten by three insects which 53 days previously had bitten patient with a typical case, on the third day of the attack. These were among a lot of mosquitos that had already infected three individuals, two of whom died of yellow fever. The result was negative. Five weeks later he received a subcutaneous injection of about ½ cc. of blood drawn from a patient with a mild case of yellow fever, on the second day of illness. Result negative. The previous history

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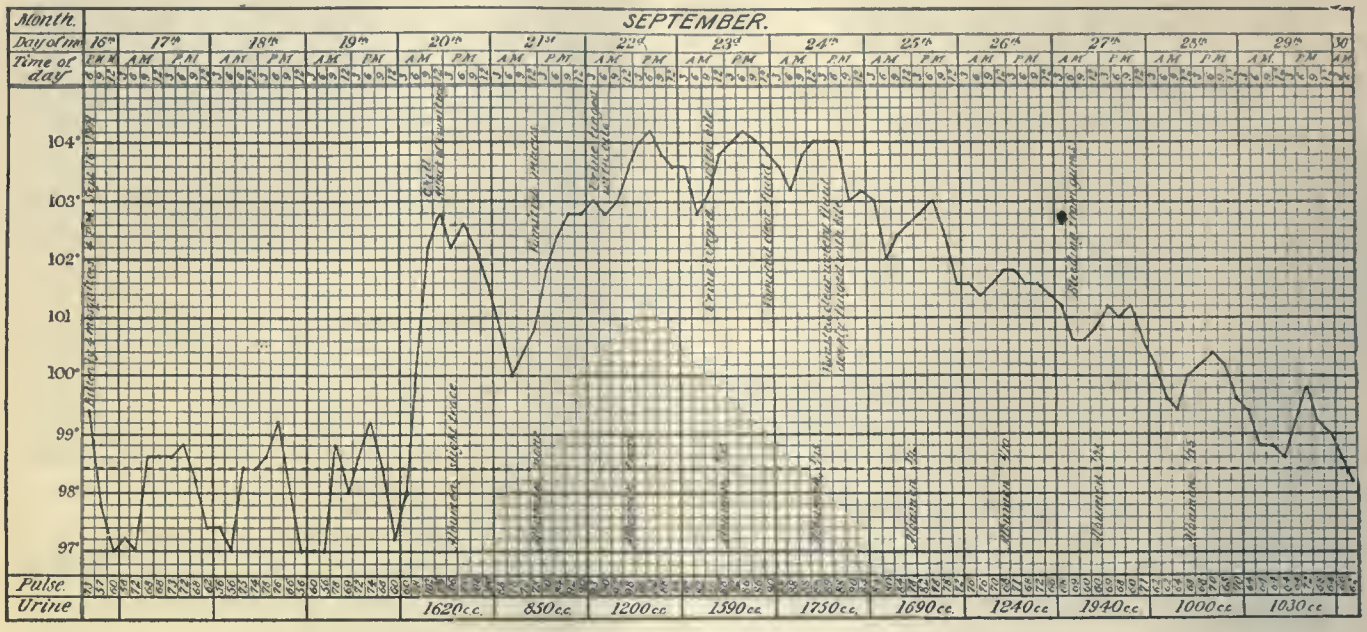

Chart I.—Yellow fever, produced by the bite of *Stegomyia fasciata*. Incubation, 72½ hours.

of this man was not satisfactory, as he had recently returned from a residence in Mexico.

September 9, 1901, A. V., Spaniard, was bitten by three mosquitos that had been applied to a mild case of yellow fever on the second day of the attack, 27 days before. Three weeks later he was again bitten by one mosquito 49 days after it had been applied to a fatal case of yellow fever, on the third day of the attack. The result of both inoculations was negative.

We give brief sketches of the two positive cases:

CASE I.—P. R. C., a Spaniard, had served in the Spanish army in the Philippines. He arrived in Havana from Spain about August 30.

On September 16, 1901, he was bitten at 4 p. m. by 4 mosquitos that had previously fed upon cases of yellow fever as follows: One had bitten a patient having a fatal case, on the third day of the disease, 53 days before, and 3 had bitten a patient having a fatal case, on the second day of illness, 34 days previously. His attack began at 4.30 p. m., September 19, after an incubation period of 72½ hours. At the onset he experienced a slight chill with rigors, and loss of appetite. Later in the evening he complained of slight frontal headache and pains in the lumbar region. On the following day the headache and backache were more severe. At 10 a. m., he vomited about six drams of slightly greenish fluid containing mucus. On the second day of the attack the gums were swollen, pale and spongy and there was soreness upon deep pressure over the epigastric and hypogastric regions; the face was flushed and the eyeballs were slightly yellow. September 24, fifth day, he was well jaundiced, epigastric and abdominal soreness were pronounced, and there was nausea with eructations. At this time an unfavorable prognosis was given by two physicians of large experience in yellow fever. Happily, with the decline of temperature on the sixth day, the symptoms were much ameliorated and the patient made an uninterrupted recovery. Albumin appeared in the urine on the third day, and persisted for 17 days. The microscope showed the presence of bile-stained epithelial and granular casts on the third and subsequent days.

Early on the second day blood was drawn from the median-basilic vein with all precaution and 10 drops were immediately added to each of four flasks containtng 200 cc. of sterile nutritive bouillon. The flasks were kept under observation in the incubator and at room temperature for 14 days without the development of any growth. At the end of that time each flask was agitated and an agar slant was freely inoculated with fibrin and fluid from its contents. These cultures remained sterile 16 days later after being kept four days in the incubator and 12 at room temperature.

On the second day, blood was drawn for the purpose of obtaining serum for filtration, but owing to an accident to the vacuum pump the experiment had to be abandoned.

Specimens of the fresh blood were examined for malarial parasites with negative results on the second and fourth days of the attack. (Chart I).

CASE II.—J. M. A., Spaniard, recently landed at Havana, was bitten at 4 p. m., October 9, by eight mosquitos that had been applied to a severe case of yellow fever (Case I) on the second day of the disease, 18 days previously. The attack which followed was mild. According to his own account he went to bed on the evening of the twelfth feeling in perfect health. He awakened about midnight with frontal headache but had no chill. October 13, 7 a. m., temperature was 102.2° F., pulse 92; complained of pain in the head and back; later in the day there was marked photophobia, pain in the region of the kidneys and slight pains in the lower extremities. The eyes were injected moderately and the gums slightly so. On the following day, October 14, the frontal headache was more severe, there was considerable soreness on pressure over the stomach and abdomen and he complained of sharp lumbar pain. An examination of the fresh blood proved negative for malarial parasites. At 4 p. m. blood was drawn from a vein at the bend of the elbow and 10 drops were inoculated into each of two flasks containing 200 cc. of sterile bouillon. One flask remained sterile, the other developed a growth which proved to be a white staphylococcus.

October 15, the gums were pale, swollen and spongy, their margins distinctly reddened, and blood could be easily pressed out from beneath the lower gums.

October 16, there was free oozing of blood from the gums and margin of the tongue. The case pursued a mild course, the temperature falling to normal at 9 p. m. of the fourth day. A trace of albumin was present in the urine passed on the morning of that day, and for a few days following hyalin and granular casts were found. The patient made a speedy recovery (Chart II).

On October 15, 11.30 a. m., at the beginning of the third day of illness, the temperature was 101° F.; 65 cc. of blood were drawn, with antiseptic precautions, from a vein at the bend of the elbow. This was placed in a sterile test-tube and set aside in the refrigerator. At 6 a. m., 5½ hours later, 19 cc. of a slightly bloodstained serum were pipetted off into another sterile tube. After the addition of an equal quantity of sterilized distilled water the diluted serum was slowly filtered through a new Berkefeld laboratory-filter that had been subjected to previous sterilization in an Arnold's sterilizer. In this way 35 cc. of a slightly bloodstained filtrate were obtained, a part of which was subsequently used for the inoculation of Cases VII, VIII and IX of this report.

The original level of the blood having been marked upon the tube into which it was drawn, a sufficient quantity of sterilized distilled water was then added to replace the 19 cc. of serum that had been pipetted off and to make up the original volume of blood. The whole, consisting of clot, remaining serum, and distilled water, was poured into a sterile vessel and whipped up with a sterilized egg-beater. The mixture, which approximately represented the partially defibrinated blood, was then divided into two parts, one of which was reserved for the inoculation ot a control subject (Case III), while the other part was placed in a double water-bath previously heated, and exposed to a temperature of 55° C. for 10 minutes. It was then removed and immediately cooled in icewater. This cooled material was subsequently used for the injection of Cases IV, V and VI.

It will thus be seen that we have at our disposal, for purposes of inoculation, three kinds of materials, derived from the blood in Case II, viz.: (*a*) The unheated and partially defibrinated blood; (*b*) the partially defibrinated blood which had been heated to a temperature of

55° C. for ten minutes, and (*c*) the diluted blood-serum which had been filtered through a Berkefeld filter. Each of these materials was used for the inoculation of one or more nonimmune individuals with the results that follow herewith:

(*a*) THE UNHEATED AND PARTIALLY DEFIBRINATED BLOOD.

CASE III.—M. G. M., Spaniard, arrived at Havana October 4, 1901. At 4 p. m., October 15, he was given a subcutaneous injection of 0.75 cc. of the unheated and partially defibrinated blood obtained from Case II, 15½ hours previously, which had been kept 5½ hours in the refrigerator and 10 hours at room temperature. The earliest symptom, frontal headache, was complained of at 6 p. m., October 20, or at the expiration of 5 days and 2 hours after inoculation. Temperature 100.6° F., pulse 80. At 3 p. m. of the same day the temperature was 98.4° F., pulse 80. At that time the patient did not complain of any discomfort and there was nothing to indicate that he was about to be taken sick. October 21, 5 p. m., nearly 24 hours from the onset, there was flushing of the face, injection of the eyes and gums, and moderately severe headache; pain in the back, and tenderness on pressure in the epigastric region made the picture complete. On the third day the face was deeply flushed, eyes congested and distinctly yellow. There was slight oozing of blood from the gums. The urine passed at 7.30 p. m. contained a distinct trace of albumin. The case was seen by the Havana Board of Yellow Fever Experts and the diagnosis confirmed. The patient passed through a mild but typical attack, the temperature touching normal on the fifth day. (Chart III.)

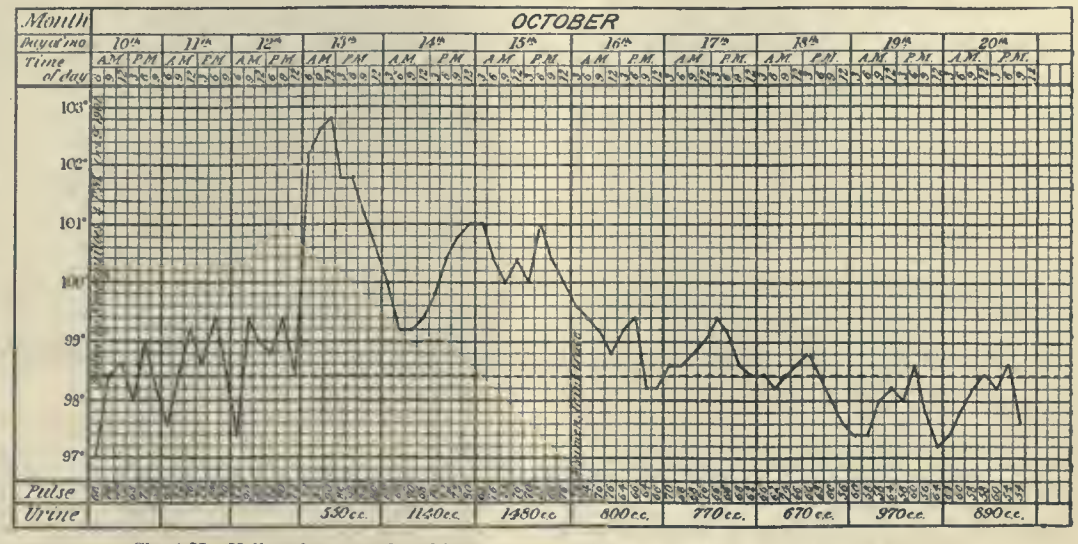

Chart II.—Yellow fever, produced by the bite of *Stegomyia fasciata*. Incubation, 80 hours.

This case, therefore, serves as a "control" for the observations which are to follow, since it demonstrates that the blood drawn from the general circulation of Case II, at the beginning of the third day, contained the specific agent of yellow fever, and, in this respect, confirms the observations which have heretofore been reported by us.[6]

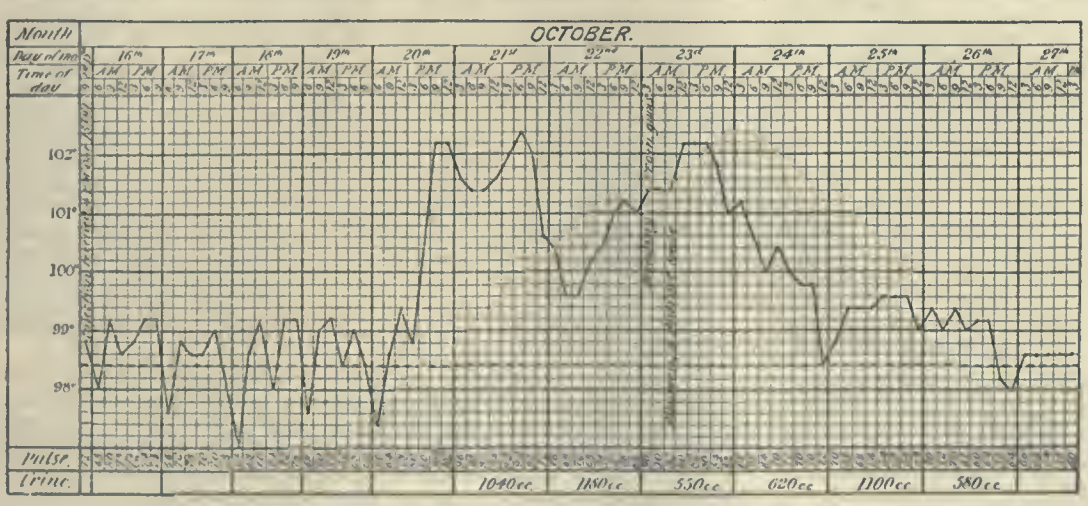

Chart III.—Yellow fever, produced by injection of 0.75 cc. of blood. Incubation, 5 days, 2 hours.

(*b*) THE PARTIALLY DEFIBRINATED BLOOD HEATED FOR 10 MINUTES AT 55°C.

CASE IV.—A. C., Spaniard, nonimmune, arrived at Havana, October 6, 1901. At 4.35 p.m., October 15, he was given subcutaneously 1.5 cc. of the partially defibrinated blood which had been subjected to a temperature of 55° C. during 10 minutes. The specimen had been drawn from Case II, 16 hours before. The result of this injection was entirely negative, as the subject remained in perfect health during the 10 days following.

CASE V.—B. F. M., Spaniard, nonimmune, arrived at Havana, October 6, 1901. At 4.45 p. m., October 15, he received a subcutaneous injection of 1.5 cc. of the same material that was used in Case IV. Result negative.

CASE VI.—S. O., Spaniard, nonimmune, arrived at Havana, October 7, 1901. At 4.50 p. m., October 15, he was given a subcutaneous injection of 1.5 cc. of the same material that was used in Cases IV and V. No rise of temperature or other symptom of ill-health followed this injection.

We desire to invite attention to the fact that the four subjects whose protocols have been given above were young Spaniards who arrived at Havana at a time when yellow fever was not present in the city; that they were carried from the quarantine camp, at Triscornia, across the bay, direct to Columbia barracks, near Quemados, Cuba, where they were kept for seven full days prior to inoculation; and that after inoculation they were kept under close daily observation for the further period of 10 days, during which time both temperature and pulse were recorded every third hour. Since under these circumstances each of the three nonimmunes (Cases IV, V and VI) received, without any disturbance to health, double the quantity of *heated* and partially defibrinated blood that sufficed when *unheated* to cause an attack of yellow fever in Case III, it follows that the specific agent present in the blood in yellow fever is destroyed, or, at least, markedly attenuated, by a temperature of 55°C. maintained for 10 minutes.

(*c*) THE DILUTED AND FILTERED SERUM.

CASE VII.—P. H., American soldier, nonimmune, received at 11 a. m., October 15, 1901, a subcutaneous injection of 3 cc. of the serum filtrate, representing 1.5 cc. of the undiluted

serum 10½ hours after the blood had been drawn from Case II. He remained in good health until 3 p. m. October 19, an interval of four days and four hours, when his face appeared flushed and his eyes somewhat injected. His temperature at this time was 101° F., his pulse 80. He did not complain of headache or other pain. From this hour his temperature declined, until at 12 o'clock midnight it registered 98° F., pulse 72. October 20, 9 a. m., temperature 100.8° F., pulse 78. Face more suffused, and slight headache complained of. Fever continued on the twenty-first, with more marked flushing of the face and injection of the eyes. The height of the primary febrile paroxysm was reached at 6 p. m. October 21. Remission occurred at 9 a. m. October 22, when the temperature dropped to 98.8° F., pulse 64. This lasted for 24 hours, and was followed by a secondary febrile paroxysm of 42 hours' duration. On the twenty-third blood was oozing from the lower gums and the eyeballs were tinged with yellow. Albumin appeared in the urine on the fourth day. The patient was visited by the Board of Experts and the diagnosis of yellow fever confirmed. Examination of the dried blood for malarial parasites was negative. The patient recovered. (Chart IV).

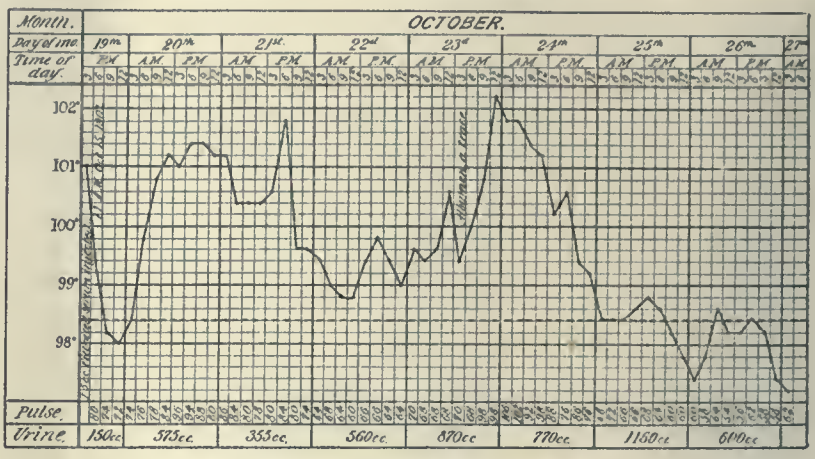

Chart IV.—Yellow fever, produced by injection of 1.5 cc. of filtered blood-serum. Incubation, 4 days, 4 hours.

CASE VIII.—A. W. C., American soldier, nonimmune, was also given at 11.05 a. m., October 15, 1901, a subcutaneous injection of 3 cc. of the diluted and filtered serum, being the equivalent of 1.5 cc. of the undiluted serum, 10½ hours after the blood had been drawn. He remained in his usual health until about noon, October 19, at which time he felt "out of sorts," and ate but little dinner. This was 4 days and 1 hour after the injection. During the afternoon he lay down and slept until 3 p. m., when he awoke with a severe headache and backache. His face was flushed. Temperature 103.6° F., pulse 102. At this hour his face and eyes were deeply congested, and from this time his symptoms were characteristic of the disease. On the twentythird his eyes were quite yellow, and general jaundice followed later. No albumin was found in this patient's urine. He was seen by the Board of Experts and his illness pronounced a typical case of yellow fever. Careful examination of the dried blood for malarial parasites was negative. The patient made a good recovery. (Chart V.)

CASE IX.—J. R. B., American, nonimmune, at 2.30 p. m., October 15, 1901, was given a subcutaneous injection of 3 cc. of the diluted and filtered serum, equal to 1.5 cc. of the undiluted serum. Fourteen hours had elapsed since the blood had been drawn from Case II.

This injection was followed by no symptoms of physical disturbance, until 3 p. m., October 19, an interval of four days and a half hour, when his temperature was 99.4° F., pulse 92. He complained of headache and flashes of heat with slight pain between the shoulders, symptoms which the subject stated were quite unusual to him. At 9 p. m., temperature 98.4° F., pulse 84. There was no further febrile disturbance and the day following the subject was in his usual good health.

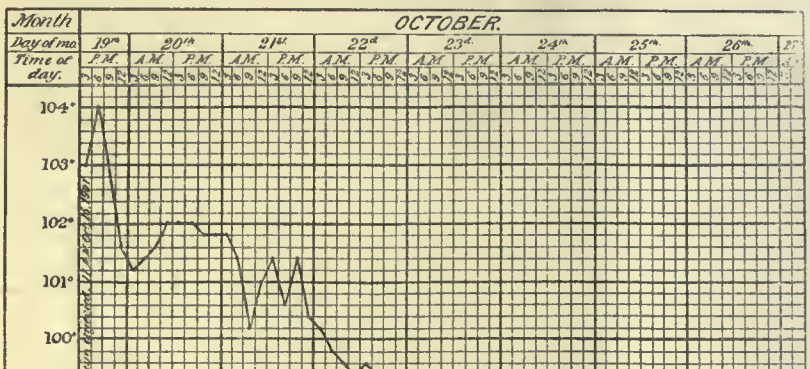

Chart V.—Yellow fever, produced by injection of 1.5 cc. of filtered blood-serum. Incubation, 4 days, 1 hour.

We thus observe that of 3 nonimmune individuals who received subcutaneously an injection of *filtered* bloodserum derived from Case II of this report, 2 developed an unmistakable attack of yellow fever, after a period of incubation of 98½ hours and 100 hours respectively, while in 1 case the result must be regarded as negative.

As already stated, the serum used for these inoculations had been slowly filtered through a new Berkefeld laboratory-filter. As soon as possible thereafter the filter was resterilized by steam and thoroughly tested as to its effectiveness in preventing the passage of bacteria. For this purpose a recent bouillon culture of *Staphylococcus pyogenes aureus* was used, of which 50 cc. were passed through the filter. The filtrate thus obtained was transferred in quantities of 10 cc. to each of two flasks containing 200 cc. of sterile bouillon, which were incubated at 37° C. for 4 days and thereafter kept at room temperature for 10 days longer, at the end of which time no growth had occurred. It appears, therefore, that the filter used for the filtration of the blood-serum in Case II was to be relied upon for the delivery of a bacteria-free filtrate.

The production of yellow fever by the injection of blood-serum that had previously been passed through a filter capable of removing all test bacteria, is, we think, a matter of extreme interest and importance. The occurrence of the disease under such circumstances, and within the usual period of incubation, might be explained in one of two ways, viz., first, upon the supposition that the serum filtrate contains a toxin of considerable potency; or, secondly, that the specific agent of yellow fever is of such minute size as to pass readily through the pores of a Berkefeld filter.

In favor of the supposition that in yellow fever an active toxin is present in the blood, may be cited the early and well marked jaundice; the free hemorrhage from the mucous membranes of the mouth and stomach, doubtless due to profound changes in capillary vessel-walls; the rapid progress of the disease to a fatal termination, the advanced fatty degeneration of the hepatic cells, as well as the marked parenchymatous changes found in the kidneys. If present in the blood this toxin would in all likelihood be found in the serum filtrate obtained from the blood, and if injected in sufficient quantity, might induce an attack of yellow fever in a susceptible individual after the usual period of incubation. In this respect it would bear analogy to the pro-

duction of tetanus in the human being, after the usual period of incubation of this disease by the subcutaneous injection of a very small quantity of tetanus toxin, as reported by Nicolas[7] in 1893, and more recently by Bolton, Fisch and Walden.[8]

Against the view that a toxin is present in the serum filtrate, we invite attention to the innocuousness of the partially defibrinated blood when heated to 55° C. for 10 minutes, as shown by the negative results in Cases IV, V and VI. Here the toxin, which must have been present in just the same quantity as in the serum filtrate obtained from this blood, appears to have been completely destroyed by the temperature above mentioned. Now, although certain bacteria are destroyed by this temperature, as yet we know of no bacterial toxin that is rendered inert by such a low degree of heat continued for so short a time. The tetanus toxin, which has been found to be the most sensitive, thus far, requires, according to Kitasato, a temperature of 60° C. for 20 minutes, or 55° C. for 1½ hours in order to destroy its activity.[9]

As a further test and in order to determine whether the serum filtrate contained something more particulate than a soluble toxin, we availed ourselves of the opportunity of observing the effect that would follow the transference to a third individual, of blood drawn from

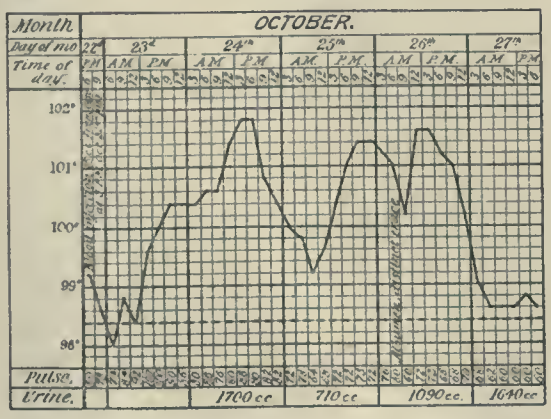

Chart VI.—Yellow fever, produced by injection of 1.5 cc. of blood. Incubation, 24 hours.

one of the patients whose attack had been occasioned by the injection of 1.5 cc. of serum filtrate (Case VII). If under these circumstances it would be found that the injection of a small quantity of blood was followed by an attack of yellow fever in a third individual, the evidence would point in the strongest manner to the presence of the specific agent of the disease in such blood, since we can hardly believe that a toxin which had undergone so great a dilution in the body of the second individual would still be capable of producing the disease.

CASE X.—October 22, 1901, 3 p. m., J. M. B., American, non-immune, who on October 15, 1901, at 2.30 p. m., had been injected with 1.5 cc. of serum filtrate with negative result (*vide* Case IX), and who still desired to have his immunity further tested, was, at the beginning of this, the eighth day after his former inoculation, given a subcutaneous injection of 1.5 cc. of blood drawn from the venous circulation of Case VII early in the fourth day of the disease. At the time of inoculation the subject's condition was quite normal. October 23, 3 p. m., after an incubation period of just 24 hours, he complained of frontal and slight basal headache and some pain between the shoulders. His temperature was 99.6° F., and pulse 100. At 6 p. m., temperature 100.4° pulse 100. Pain in the back quite severe. At 10.15 p. m. he suffered a slight chill. On the following morning the face was flushed and the eyes and gums injected; there was sharp frontal headache and some photophobia. The height of the primary paroxysm was reached at the end of 23 hours. Remission occurred at 9 a. m., October 25, and was followed by a second febrile paroxysm of 45 hours' duration. On the third day, during the secondary fever, the patient presented the typical picture of a mild case of yellow fever; the face was deeply flushed, eyes well injected and slightly yellow; there was sharp headache, and epigastric tenderness and pain in the lower extremities. Heller's test showed albumin in the urine drawn on the fourth day. His fever subsided on the latter day and he made a prompt recovery. The case was seen by the Board of Experts and the diagnosis confirmed. (Chart VI.)

In considering this individual's attack, his infection must be attributed either to the injection of the serum filtrate derived from Case II, in which event the onset of his disease was postponed until the commencement of the ninth day after inoculation, or to the injection of blood obtained from Case VII, after a period of incubation of 24 hours.

In our own experience[10] and that of Guitéras[11] of 22 cases of experimental yellow fever, following the bite of the mosquito, in which the period of incubation was definitely and accurately ascertained, the longest period was six days and one hour, and the shortest period two days and 13 hours. If we take the cases produced by the injection of blood, seven in number, exclusive of the case under consideration, the longest period was five days and two hours (Case III of this report) and the shortest 41 hours.

In view of these data, we believe we are justified in expressing the opinion that the source of infection in Case X must be attributed to the injection of blood drawn from Case VII, rather than to the injection of the filtered serum derived from the blood in Case II; and further, that the blood in Case VII contained the specific agent of yellow fever, which had, therefore, passed through the filter along with the filtrate with which this latter individual had been inoculated.

The important questions which naturally arise from the foregoing experiments must be left for future observations to determine.

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[9] Zeitschrift für Hygiene, 1901, Bd. x, S. 283.
[10] Loc. cit.
[11] Loc. cit.

OBSERVATIONS CONCERNING THE POSSIBLE INFECTIOUSNESS OF MEAT AND MILK FROM TUBERCULOUS ANIMALS.[1]

BY

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The causative agent of tuberculosis is an organism of extreme dissemination and one which shows an adaptability to widely varying conditions of temperature and ailment.

As with the higher forms of life, influence of environment upon it is shown in modifications of form and temporary inhibition of vitality and reproductive activity. Yet the various families of this bacillus, whether they be piscine, avian, human or bovine, which have accustomed themselves to life under their own peculiar food and temperature conditions, may, through the careful direction of the bacteriologist, be made to participate in a grand reunion, where each thrives upon

[1] Read by invitation before the Oregon State Medical Society, Portland, September 27.